

=> s levosimendan/cn

L1 1 LEVOSIMENDAN/CN

=> d l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS

RN 141505-33-1 REGISTRY

CN Propanedinitrile, [[4-[(4R)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl]phenyl]hydrazono]- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Propanedinitrile, [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-, (R)-

OTHER NAMES:

CN (-)-OR 1259

CN (R)-Simendan

CN **Levosimendan**

CN OR 1259

CN Simdax

FS STEREOSEARCH

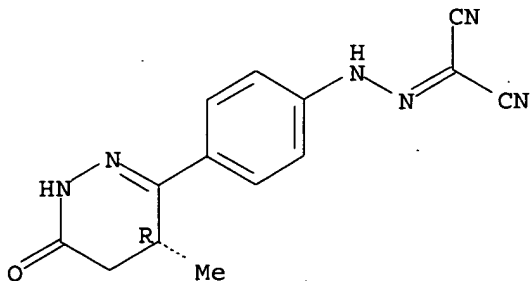
MF C14 H12 N6 O

SR World Health Organization

LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK\*, PHAR, PHARMASEARCH, PROMT, SYNTHLINE, TOXCENTER, USAN, USPATFULL

(\*File contains numerically searchable property data)

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

111 REFERENCES IN FILE CA (1957 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

114 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> FIL REGISTRY

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

8.70

9.54

FILE 'REGISTRY' ENTERED AT 11:20:51 ON 27 MAY 2003

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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Property values tagged with IC are from the ZIC/VINITI data file

provided by InfoChem.

STRUCTURE FILE UPDATES: 26 MAY 2003 HIGHEST RN 520505-31-1  
DICTIONARY FILE UPDATES: 26 MAY 2003 HIGHEST RN 520505-31-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP  
PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> SET TERMSET E#

SET COMMAND COMPLETED

=> DEL SEL Y

=> SEL L1 1 RN

E1 THROUGH E1 ASSIGNED

=> S E1/RN

L2 1 141505-33-1/RN

=> SET TERMSET LOGIN

SET COMMAND COMPLETED

=> FIL MRCK

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.48	10.02

FILE 'MRCK' ENTERED AT 11:20:56 ON 27 MAY 2003  
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FILE COVERS FROM LATE 19TH CENTURY TO PRESENT. LAST UPDATE: NOV 2002

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Office.

=> S L2

L3 1 L2

=> DIS L3 1 SAM

L3 ANSWER 1 OF 1 MRCK COPYRIGHT (C) 2003 Merck and Co., Inc.,  
Whitehouse Station, New Jersey, USA. All rights reserved.

MERCK Number (MNO): 5491  
CAS Registry No. (RN): 141505-33-1  
MERCK Index Name (MIN): Levosimendan  
Molecular Form. (MF): C14 H12 N6 O

Available Display Fields (FA):

Code	Field Name
RN	CAS Registry Number
CN	Chemical Name
CN	Chemical Name (Drug Code)
CN	Chemical Name (CAS Index Name)
CN	Chemical Name (Synonym)
CN	Chemical Name (Trade Name)
COMP	Elemental Composition (by weight)
MP	Melting Point
MF	Molecular Formula
MW	Molecular Weight
ORP	Optical Rotatory Power
OCPP	Other Chemical and Physical Properties
RPN	Referenced Patent Number
THER	Therapeutic Category
TOX	Toxicity

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.31

10.33

FILE 'CAPLUS' ENTERED AT 11:21:44 ON 27 MAY 2003

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FILE COVERS 1907 - 27 May 2003 VOL 138 ISS 22

FILE LAST UPDATED: 26 May 2003 (20030526/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l1

L4 113 L1

=> s l4 and pH

1147876 PH

L5 8 L4 AND PH

=> d l5 1-8

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2002:470297 CAPLUS

DN 138:242993

TI Development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules

AU Kortejarvi, H.; Mikkola, J.; Backman, M.; Antila, S.; Marvola, M.

CS Orion Pharma, Espoo, 02101, Finland  
SO International Journal of Pharmaceutics (2002), 241(1), 87-95  
CODEN: IJPHDE; ISSN: 0378-5173  
PB Elsevier Science B.V.  
DT Journal  
LA English  
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:906809 CAPLUS  
DN 137:72913  
TI Effects of levosimendan, a novel inotropic calcium-sensitizing drug, in  
experimental septic shock  
AU Oldner, Anders; Konrad, David; Weitzberg, Eddie; Rudehill, Anders; Rossi,  
Patrik; Wanecek, Michael  
CS Department of Surgical Sciences, Section of Anaesthesiology and Intensive  
Care Medicine, Karolinska Institute, Stockholm, Swed.  
SO Critical Care Medicine (2001), 29(11), 2185-2193  
CODEN: CCMDC7; ISSN: 0090-3493  
PB Lippincott Williams & Wilkins  
DT Journal  
LA English  
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS  
AN 2000:719370 CAPLUS  
DN 134:76296  
TI Transdermal delivery of levosimendan  
AU Valjakka-Koskela, R.; Hirvonen, J.; Monkkonen, J.; Kiesvaara, J.; Antila,  
S.; Lehtonen, L.; Urtti, A.  
CS Pharmaceutical Development Department, Orion Corporation Orion Pharma,  
Kuopio, 70701, Finland  
SO European Journal of Pharmaceutical Sciences (2000), 11(4), 343-350  
CODEN: EPSCED; ISSN: 0928-0987  
PB Elsevier Science Ireland Ltd.  
DT Journal  
LA English  
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS  
AN 2000:622118 CAPLUS  
DN 133:344385  
TI Levosimendan improves diastolic and systolic function in failing human  
myocardium  
AU Janssen, P. M. L.; Datz, N.; Zeitz, O.; Hasenfuss, G.  
CS Abt. Kardiologie und Pneumologie, Universitat Gottingen, Gottingen,  
Germany  
SO European Journal of Pharmacology (2000), 404(1/2), 191-199  
CODEN: EJPHAZ; ISSN: 0014-2999  
PB Elsevier Science B.V.  
DT Journal  
LA English  
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS  
AN 2000:191448 CAPLUS  
DN 133:26467  
TI Further Evidence for the Cardiac Troponin C Mediated Calcium Sensitization  
by Levosimendan: Structure-response and Binding Analysis with Analogs of  
Levosimendan

AU Levijoki, Jouko; Pollesello, Piero; Kaivola, Juha; Tilgmann, Carola;  
 Sorsa, Tia; Annila, Arto; Kilpelainen, Ilkka; Haikala, Heimo  
 CS Department of Drug Discovery & Pharmacology, Orion Pharma, Preclinical  
 Research, Espoo, FIN-02101, Finland  
 SO Journal of Molecular and Cellular Cardiology (2000), 32(3), 479-491  
 CODEN: JMCDAJ; ISSN: 0022-2828  
 PB Academic Press  
 DT Journal  
 LA English  
 RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS  
 AN 1999:811225 CAPLUS  
 DN 132:40660  
 TI A reference compound for use in the analysis of levosimendan batches  
 IN Backstrom, Reijo; Heinonen, Tuula; Hauta-Aho, Tuula  
 PA Orion Corporation, Finland  
 SO PCT Int. Appl., 13 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9965888	A2	19991223	WO 1999-FI539	19990618
	WO 9965888	A3	20000127		
	W: AE, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FI 9801428	A	19991219	FI 1998-1428	19980618
	CA 2334864	AA	19991223	CA 1999-2334864	19990618
	AU 9947863	A1	20000105	AU 1999-47863	19990618
	AU 755699	B2	20021219		
	BR 9911230	A	20010306	BR 1999-11230	19990618
	EP 1087956	A2	20010404	EP 1999-931312	19990618
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NZ 508557	A	20020531	NZ 1999-508557	19990618
	JP 2002518383	T2	20020625	JP 2000-554714	19990618
	NO 2000006444	A	20001215	NO 2000-6444	20001215
	US 6340764	B1	20020122	US 2001-719806	20010220
PRAI	FI 1998-1428	A	19980618		
	WO 1999-FI539	W	19990618		

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS  
 AN 1997:10659 CAPLUS  
 DN 126:112688  
 TI Enantiomeric bioanalysis of simendan and levosimendan by chiral high-performance liquid chromatography  
 AU Wikberg, Tom; Korkolainen, Tapio; Karlsson, Marianne  
 CS Orion-Farmos, Orion Res., Espoo, FIN-02101, Finland  
 SO Chirality (1996), 8(7), 511-517  
 CODEN: CHRLEP; ISSN: 0899-0042  
 PB Wiley-Liss  
 DT Journal  
 LA English

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS  
 AN 1995:521629 CAPLUS  
 DN 122:255986  
 TI Troponin C-mediated calcium sensitization induced by levosimendan does not

impair relaxation  
 AU Haikala, Heimo; Nissinen, Erkki; ERtemadzadeh, Ehsan; Levijoki, Jouko;  
 Linden, Inge-Britt  
 CS Orion-Farmos, Orion Research, Espoo, Finland  
 SO Journal of Cardiovascular Pharmacology (1995), 25(5), 794-801  
 CODEN: JCPCDT; ISSN: 0160-2446  
 PB Lippincott-Raven  
 DT Journal  
 LA English

=> d 15 1-8 full

'FULL' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS ----- GI and AB  
 ALL ----- BIB, AB, IND, RE  
 APPS ----- AI, PRAI  
 BIB ----- AN, plus Bibliographic Data and PI table (default)  
 CAN ----- List of CA abstract numbers without answer numbers  
 CBIB ----- AN, plus Compressed Bibliographic Data  
 DALL ----- ALL, delimited (end of each field identified)  
 DMAX ----- MAX, delimited for post-processing  
 FAM ----- AN, PI and PRAI in table, plus Patent Family data  
 FBIB ----- AN, BIB, plus Patent FAM  
 IND ----- Indexing data  
 IPC ----- International Patent Classifications  
 MAX ----- ALL, plus Patent FAM, RE  
 PATS ----- PI, SO  
 SAM ----- CC, SX, TI, ST, IT  
 SCAN ----- CC, SX, TI, ST, IT (random display, no answer numbers;  
 SCAN must be entered on the same line as the DISPLAY,  
 e.g., D SCAN or DISPLAY SCAN)  
 STD ----- BIB, IPC, and NCL  
  
 IABS ----- ABS, indented with text labels  
 IALL ----- ALL, indented with text labels  
 IBIB ----- BIB, indented with text labels  
 IMAX ----- MAX, indented with text labels  
 ISTD ----- STD, indented with text labels  
  
 OBIB ----- AN, plus Bibliographic Data (original)  
 OIBIB ----- OBIB, indented with text labels  
  
 SBIB ----- BIB, no citations  
 SIBIB ----- IBIB, no citations  
  
 HIT ----- Fields containing hit terms  
 HITIND ----- IC, ICA, ICI, NCL, CC and index field (ST and IT)  
 containing hit terms  
 HITRN ----- HIT RN and its text modification  
 HITSTR ----- HIT RN, its text modification, its CA index name, and  
 its structure diagram  
 HITSEQ ----- HIT RN, its text modification, its CA index name, its  
 structure diagram, plus NTE and SEQ fields  
 FHITSTR ----- First HIT RN, its text modification, its CA index name, and  
 its structure diagram  
 FHITSEQ ----- First HIT RN, its text modification, its CA index name, its  
 structure diagram, plus NTE and SEQ fields  
 KWIC ----- Hit term plus 20 words on either side  
 OCC ----- Number of occurrence of hit term and field in which it occurs

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codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

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ENTER DISPLAY FORMAT (BIB):all

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2002:470297 CAPLUS

DN 138:242993

TI Development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules

AU Kortejarvi, H.; Mikkola, J.; Backman, M.; Antila, S.; Marvola, M.

CS Orion Pharma, Espoo, 02101, Finland

SO International Journal of Pharmaceutics (2002), 241(1), 87-95

CODEN: IJPHDE; ISSN: 0378-5173

PB Elsevier Science B.V.

DT Journal

LA English

CC 63-5 (Pharmaceuticals)

AB The aim of this study was to investigate the possibility of developing different levels of correlation between in vitro release and in vivo absorption rate for four modified-release levosimendan capsule formulations. Differences and similarities in the in vitro dissoln. curves were compared with pharmacokinetic parameters describing absorption rate. Formulations F, G, H and I differed in the amts. of the delaying excipients alginic acid and hydroxypropyl Me cellulose. In vitro release rate was studied by the USP basket method using the following conditions: pH 5.8 or 7.4 and a rotation speed of 50 or 100 rpm. In vivo bioavailability was tested in nine healthy male volunteers and the fractions absorbed were calcd. by the Wagner-Nelson method. Dissoln. conditions pH 5.8 and a rotation speed of 100 rpm predicted best the similarities and differences in absorption rates among different formulations; and levels C and B correlation coeffs. were 0.85 and 0.97, resp. For formulation H level A correlation ( $r = 0.997$ ) was found when in vitro lag time was 0.2 h and time scale factor 1.9. This study indicated that dissoln. tests developed can be used as a surrogate for human bioequivalence studies, for development processes of final com. products, to ensure batch to batch bioequivalence and in the future in possible scale-up and post approval change cases for modified-release levosimendan formulation H.

ST bioavailability levosimendan capsule

IT Drug delivery systems

(capsules, modified-release; development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules)

IT Dissolution

Drug bioavailability

Human

(development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules)

IT 57-11-4, Stearic acid, biological studies 9004-65-3, Hydroxypropyl methyl cellulose 9005-32-7, Alginic acid

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules)

IT 141505-33-1, Levosimendan

RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(development of level A, B and C in vitro-in vivo correlations for

modified-release levosimendan capsules)  
IT 9004-34-6, Cellulose, biological studies  
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(microcryst.; development of level A, B and C in vitro-in vivo  
correlations for modified-release levosimendan capsules)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

- (1) Amidon, G; Pharm Res 1995, V3, P413
- (2) Antila, S; Eur J Pharm Sci 1999, V9, P85 CAPLUS
- (3) Brockmeier, D; Areneim Forsch/Drug Res 1983, V33, P598 MEDLINE
- (4) Cardot, J; Eur J Metab Pharmacokinet 1993, V1, P113
- (5) Cutler, D; Int J Pharm 1997, V158, P185 CAPLUS
- (6) Hernandez, R; Int J Pharm 1996, V139, P45 CAPLUS
- (7) Karlsson, M; Biomed Chromatogr 1997, V11, P54 CAPLUS
- (8) Leeson, L; Drug Inf J 1995, V29, P903
- (9) Lilleberg, J; J Cardiovasc Pharmacol 1995, V26(Suppl 1), P63
- (10) Moore, J; Pharm Tech 1996, V20(6), P64
- (11) Munday, D; Int J Pharm 1995, V118, P251 CAPLUS
- (12) Sandell, E; J Cardiovasc Pharmacol 1995, V26, PS57 CAPLUS
- (13) Skelly, J; Pharm Res 1990, V9, P975
- (14) Sunberg, S; Int J Clin Pharmacol Ther 1998, V36, P629
- (15) Takahashi, R; Eur J Pharmacol 2000, V400, P103 CAPLUS
- (16) Wagner, J; J Pharm Sci 1964, V53, P1392 CAPLUS
- (17) Yu, Z; Biopharm Drug Dispos 1996, V17, P259 CAPLUS

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2001:906809 CAPLUS

DN 137:72913

TI Effects of levosimendan, a novel inotropic calcium-sensitizing drug, in  
experimental septic shock

AU Oldner, Anders; Konrad, David; Weitzberg, Eddie; Rudehill, Anders; Rossi,  
Patrik; Wanecek, Michael

CS Department of Surgical Sciences, Section of Anaesthesiology and Intensive  
Care Medicine, Karolinska Institute, Stockholm, Swed.

SO Critical Care Medicine (2001), 29(11), 2185-2193

CODEN: CCMDC7; ISSN: 0090-3493

PB Lippincott Williams & Wilkins

DT Journal

LA English

CC 1-8 (Pharmacology)

AB Levosimendan is a novel inodilator that improves cardiac contractility by  
sensitizing troponin C to calcium. This drug has proved to be effective  
in treating advanced congestive heart failure but has not been evaluated  
in septic settings. The purpose of the present study was to study the  
effects of this drug in a porcine model of endotoxemia in a prospective  
exptl. study. All animals (fourteen land-race pigs) were anesthetized and  
catheterized for measurement of central and pulmonary hemodynamics.  
Ultrasonic flow probes were placed around the renal artery and portal vein  
to measure blood flow. A tonometer was placed in the ileum to measure  
mucosal pH. Levosimendan was given to six animals as a bolus  
(200 .mu.g.cntdot.kg-1) followed by a continuous infusion (200  
.mu.g.cntdot.kg-1-hr-1). Thirty minutes after onset of levosimendan  
treatment, all animals received endotoxin (20 .mu.g.cntdot.kg-1-hr-1 for 3  
h). At baseline, levosimendan induced a systemic vasodilation with a  
redn. in blood pressure and an increase in heart rate. A tendency to an  
increase in cardiac index did not reach statistical significance (p =  
.055). Cardiac index and systemic oxygen delivery were markedly improved  
in the levosimendan group during endotoxemia. Systemic vascular  
resistance and blood pressure were reduced in the levosimendan group. The  
latter parameter, however, was only different from the control group  
during the initial phase of endotoxin shock but not at the late, most  
pronounced phase of shock. Levosimendan also efficiently attenuated  
endotoxin-induced pulmonary hypertension. Portal venous blood flow and



gut oxygen delivery were improved, but no concomitant redn. in endotoxin-induced intestinal mucosal acidosis was obsd. Renal blood flow was unaffected, as was the endotoxin-induced increase in plasma endothelin-1-like immunoreactivity. These findings support previous reports of calcium desensitization as a potential component in septic myocardial depression. Furthermore, the vasodilatory properties of this drug were well tolerated in the current model of hypodynamic endotoxin shock, and they may have contributed to improved regional blood flow as seen in the gut as well as improved systemic perfusion by means of reduced biventricular afterload. Pretreatment with levosimendan in pigs subjected to endotoxin shock improved cardiac output and systemic and gut oxygen delivery. In addn., pulmonary hypertension largely was attenuated without any adverse effects on gas exchange. These results are promising in several aspects, but the role of levosimendan in the treating circulatory failure in sepsis remains to be established.

- ST inotropic calcium sensitizer levosimendan septic shock heart failure
- IT Heart, disease
  - (failure; inotropic calcium-sensitizing drug levosimendan effect in septic shock)
- IT Cardiovascular system
  - Circulation
  - Endotoxemia
  - Inotropics
  - Vasodilators
  - (inotropic calcium-sensitizing drug levosimendan effect in septic shock)
- IT Heart, disease
  - (myocarditis, septic; inotropic calcium-sensitizing drug levosimendan effect in septic shock)
- IT Antihypertensives
  - Hypertension
  - (pulmonary; inotropic calcium-sensitizing drug levosimendan effect in septic shock)
- IT Shock (circulatory collapse)
  - (septic; inotropic calcium-sensitizing drug levosimendan effect in septic shock)
- IT 7440-70-2, Calcium, biological studies
  - RL: BSU (Biological study, unclassified); BIOL (Biological study)
  - (inotropic calcium-sensitizing drug levosimendan effect in septic shock)
- IT 141505-33-1, Levosimendan
  - RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
  - (inotropic calcium-sensitizing drug levosimendan effect in septic shock)

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

- (1) Angus, D; Crit Care Med 2000, V28, PA48
- (2) Archer, S; Adv Exp Med Biol 2000, V475, P219 CAPLUS
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- (5) Carrico, C; Arch Surg 1986, V121, P196 MEDLINE
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- (15) Hollenberg, S; J Heart Lung Transplant 1997, V16, PS7 MEDLINE
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- (19) Landry, D; J Clin Invest 1992, V89, P2071 CAPLUS
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- (23) Nicklas, J; Am J Cardiol 1999, V83, P12 CAPLUS
- (24) Oldner, A; Br J Pharmacol 1999, V127, P1793 CAPLUS
- (25) Oldner, A; Gut 1998, V42, P696 CAPLUS
- (26) Oldner, A; Splanchnic Organ Homeostasis in Experimental Endotoxin Shock:  
With Special Reference to the Endothelin and Renin-Angiotensin Systems 1999
- (27) Pagel, P; Br J Pharmacol 1996, V119, P609 CAPLUS
- (28) Rubanyi, G; Pharmacol Rev 1994, V46, P325 CAPLUS
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- (31) Udvary, E; Br J Pharmacol 1995, V114, P656 CAPLUS
- (32) Vanelli, G; Exp Physiol 1995, V80, P167 CAPLUS
- (33) Wanecek, M; Eur J Pharmacol 2000, V407, P1 CAPLUS
- (34) Wanecek, M; Shock 1997, V7, P364 MEDLINE
- (35) Yasuda, S; Circ Res 1997, V81, P1011 CAPLUS
- (36) Yokoshiki, H; J Pharmacol Exp Ther 1997, V283, P375 CAPLUS

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2000:719370 CAPLUS

DN 134:76296

TI Transdermal delivery of levosimendan

AU Valjakka-Koskela, R.; Hirvonen, J.; Monkkonen, J.; Kiesvaara, J.; Antila, S.; Lehtonen, L.; Urtti, A.

CS Pharmaceutical Development Department, Orion Corporation Orion Pharma, Kuopio, 70701, Finland

SO European Journal of Pharmaceutical Sciences (2000), 11(4), 343-350  
CODEN: EPSCED; ISSN: 0928-0987

PB Elsevier Science Ireland Ltd.

DT Journal

LA English

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1

AB The aim of this study was to det. if transdermal penetration of levosimendan, a novel pos. inotropic drug, was enhanced and controlled by formulation modifications. Penetration of levosimendan across human epidermis in vitro was detd. using abdominal excised skin and diffusion cells. Predicted steady-state plasma concns. of levosimendan were estd. using permeabilities and pharmacokinetic parameters of levosimendan. For penetration enhancement we used different pH values, co-solvents, cyclodextrins, surfactants, penetration enhancers, liposomes, and iontophoresis. Sodium lauryl sulfate, ethanol, oleic acid, and soya phosphatidylcholine or their combinations clearly increased levosimendan permeation across the skin in vitro. Iontophoresis was also an efficient method to increase transdermal permeation of levosimendan. A hydrophilic co-solvent/penetration enhancer is needed to achieve better permeability of levosimendan across the skin. Thus, transdermal delivery of levosimendan can be significantly increased by formulation modification. Based on kinetic calcns.; therapeutic plasma concns. may be achievable transdermally.

ST transdermal delivery levosimendan

IT Skin

(epidermis; transdermal delivery of levosimendan)

IT Biological transport

(permeation; transdermal delivery of levosimendan)

IT Phosphatidylcholines, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(soya; transdermal delivery of levosimendan)

IT Critical micelle concentration

Drug bioavailability

Iontophoresis

Permeation enhancers

Skin

Solubilization

(transdermal delivery of levosimendan)

IT 141505-33-1, Levosimendan

RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(transdermal delivery of levosimendan)

IT 64-17-5, Ethanol, biological studies 112-80-1, Oleic acid, biological studies 151-21-3, Sodium lauryl sulfate, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(transdermal delivery of levosimendan)

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L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2000:622118 CAPLUS

DN 133:344385

TI Levosimendan improves diastolic and systolic function in failing human myocardium

AU Janssen, P. M. L.; Datz, N.; Zeitz, O.; Hasenfuss, G.

CS Abt. Kardiologie und Pneumologie, Universitat Gottingen, Gottingen, Germany

SO European Journal of Pharmacology (2000), 404(1/2), 191-199  
CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier Science B.V.

DT Journal

LA English

CC 1-8 (Pharmacology)

AB Ca<sup>2+</sup>-sensitizers increase myocardial contractility, but may worsen diastolic dysfunction. Levosimendan, through its unique troponin-C interaction, may preserve diastolic function. We investigated the effects of levosimendan (10<sup>-7</sup>-10<sup>-5</sup> M) on diastolic and systolic function in multicellular cardiac muscle preps. from end-stage failing human hearts (1 and 2.5 Hz, 37.degree.C, 1.25 mM [Ca<sup>2+</sup>], pH 7.4). Levosimendan improved systolic function: at 1 Hz, developed force (Fdev) increased from 13.84.+-.3.27 to 16.40.+-.3.57 (10<sup>-7</sup> M, P<0.05), while

diastolic force (Fdia) decreased from 5.32. $\pm$ .0.67 to 4.94. $\pm$ .0.61 mN/mm2 (P<0.05). Under control conditions, the increase in stimulation frequency from 1 to 2.5 Hz resulted in a decrease in Fdev of -0.51. $\pm$ .1.80 mN/mm2 (neg. force-frequency relationship). Levosimendan improved this relationship: at 10<sup>-7</sup> M, this change became pos. (+1.81. $\pm$ .2.06 mN/mm2, P<0.05). Diastolic function was markedly improved in the presence of levosimendan; the increase in Fdia of 1.56. $\pm$ .0.42 mN/mm2 (control) was attenuated to 0.70. $\pm$ .0.19 mN/mm2 (P<0.05). To allow for a more detailed anal., prepns. were sometimes divided into two groups, based on their force-frequency behavior. Twitch timing parameters were accelerated by levosimendan in prepns. with a neg. force-frequency relationship. Levosimendan improves both systolic and diastolic function in failing human myocardium. Effects are even more pronounced at higher heart rates and under prevailing diastolic dysfunction.

ST levosimendan diastolic systolic function heart failure

IT Blood pressure

(diastolic; levosimendan improves diastolic and systolic function in failing human myocardium)

IT Heart, disease

(failure; levosimendan improves diastolic and systolic function in failing human myocardium)

IT Cardiac contraction

Inotropics

(levosimendan improves diastolic and systolic function in failing human myocardium)

IT Blood pressure

(systolic; levosimendan improves diastolic and systolic function in failing human myocardium)

IT 141505-33-1, Levosimendan

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(levosimendan improves diastolic and systolic function in failing human myocardium)

IT 7440-70-2, Calcium, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(sensitizers; levosimendan improves diastolic and systolic function in failing human myocardium)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2000:191448 CAPLUS

DN 133:26467

TI Further Evidence for the Cardiac Troponin C Mediated Calcium Sensitization by Levosimendan: Structure-response and Binding Analysis with Analogs of Levosimendan

AU Levijoki, Jouko; Pollesello, Piero; Kaivola, Juha; Tilgmann, Carola; Sorsa, Tia; Annala, Arto; Kilpelainen, Ilkka; Haikala, Heimo

CS Department of Drug Discovery & Pharmacology, Orion Pharma, Preclinical Research, Espoo, FIN-02101, Finland

SO Journal of Molecular and Cellular Cardiology (2000), 32(3), 479-491  
CODEN: JMCDAJ; ISSN: 0022-2828

PB Academic Press

DT Journal

LA English

CC 1-3 (Pharmacology)

AB Levosimendan, an inodilatory drug discovered using troponin C as a target protein, has a cardiac effect deriving from the calcium sensitization of contractile proteins. The aim of this study was to give further evidence that levosimendan binds to cardiac troponin C and that the binding involves amino acid residues on helix. epsilon. of the N-terminal domain of this calcium-binding protein. Nine org. mols., obtained by chem. modification of levosimendan, were tested both for their calcium-dependent binding to troponin C and troponin complex affinity HPLC columns, and for their ability to increase the calcium sensitivity of myofilaments in cardiac skinned fibers. A good correlation between the calcium sensitization and the calcium-dependent binding to troponin complex ( $r=0.90$ ) and to cardiac troponin C ( $r=0.91$ ) for the analogs of levosimendan was shown. In addn., the effect of levosimendan on the calcium-induced conformational changes in native and point-mutated cTnC was studied. Cys84 Ser, Asp87 Lys and Asp88 Ala point-mutated cTnC were shown to maintain a high affinity to calcium, but their  $Ca^{2+}$  titrn. curves were not influenced by levosimendan as for the native protein. Finally, it was demonstrated that the NMR chem. shifts of the terminal Me groups of Met47, Met81, and Met85 on calcium-satd. cTnC were changed after addn. of levosimendan in water soln. at pH 7.4. This effect was not seen when adding an analog of levosimendan, which did not bind to the troponin C affinity HPLC column and did not increase the calcium-induced tension in cardiac skinned fibers. (c) 2000 Academic Press.

ST levosimendan analog heart troponin calcium sensitization; structure activity levosimendan inotropic calcium troponin

IT Troponins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(C; cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)

IT Inotropics

Structure-activity relationship

(cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(contractile; cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of

levosimendan)

IT 306-18-3 131741-03-2 131741-04-3 131741-19-0 131741-25-8  
 131741-42-9 141505-33-1, Levosimendan 274263-64-8  
 274263-65-9  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)

IT 7440-70-2, Calcium, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (sensitization; cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)

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L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 1999:811225 CAPLUS

DN 132:40660

TI A reference compound for use in the analysis of levosimendan batches

IN Backstrom, Reijo; Heinonen, Tuula; Hauta-Aho, Tuula

PA Orion Corporation, Finland

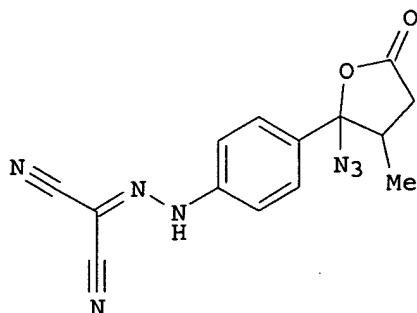
SO PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DT Patent  
LA English  
IC ICM C07D307-00  
CC 64-3 (Pharmaceutical Analysis)  
Section cross-reference(s): 28  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9965888	A2	19991223	WO 1999-FI539	19990618
	WO 9965888	A3	20000127		
	W: AE, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FI 9801428	A	19991219	FI 1998-1428	19980618
	CA 2334864	AA	19991223	CA 1999-2334864	19990618
	AU 9947863	A1	20000105	AU 1999-47863	19990618
	AU 755699	B2	20021219		
	BR 9911230	A	20010306	BR 1999-11230	19990618
	EP 1087956	A2	20010404	EP 1999-931312	19990618
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NZ 508557	A	20020531	NZ 1999-508557	19990618
	JP 2002518383	T2	20020625	JP 2000-554714	19990618
	NO 2000006444	A	20001215	NO 2000-6444	20001215
	US 6340764	B1	20020122	US 2001-719806	20010220
PRAI	FI 1998-1428	A	19980618		
	WO 1999-FI539	W	19990618		

GI



I

AB I is used as a ref. compd. in the detn. of potentially genotoxic impurities in levosimendan samples. The invention also relates to an analytic method for the detn. of potentially genotoxic impurities in levosimendan samples wherein I is used as a ref. compd. Levosimendan is a medicament useful in the treatment of heart failure. To a a soln. of 153 g 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone in 750 mL acetic acid was slowly added 210 g of sodium nitrite at 10-20.degree.. The reaction mixt. was poured rapidly to 20.degree. soln. of 150g malononitrile in 1500 mL water and stirred at 20-25.degree. for 60 min, then filtered and washed with water. The wet solid was extd. successively with THF and Et acetate, then dried and the solvent evapd. The residue was purified to obtain [4-(2-azido-3-methyl-5-oxotetrahydro-furan-2-yl)phenyl]hydrazonolpropanedinitrile (II) (a mixt. of diastereomers). II was used as ref. compd. in HPLC of levosimendan with UV detection at 360 nm and the mobile phase of acetonitrile and phosphate buffer pH = 2.1.

ST pyridazinyl deriv ref levosimendan analysis

IT HPLC  
Mutagens  
(ref. compd. for use in anal. of levosimendan batches)

IT 252638-01-0P  
RL: ANT (Analyte); SPN (Synthetic preparation); ANST (Analytical study);  
PREP (Preparation)  
(ref. compd. for use in anal. of levosimendan batches)

IT 141505-33-1, Levosimendan  
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL  
(Biological study); USES (Uses)  
(ref. compd. for use in anal. of levosimendan batches)

IT 109-77-3, Malononitrile 7632-00-0, Sodium nitrite  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(ref. compd. for use in anal. of levosimendan batches)

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS  
AN 1997:10659 CAPLUS  
DN 126:112688  
TI Enantiomeric bioanalysis of simendan and levosimendan by chiral  
high-performance liquid chromatography  
AU Wikberg, Tom; Korkolainen, Tapio; Karlsson, Marianne  
CS Orion-Farmos, Orion Res., Espoo, FIN-02101, Finland  
SO Chirality (1996), 8(7), 511-517  
CODEN: CHRLEP; ISSN: 0899-0042  
PB Wiley-Liss  
DT Journal  
LA English  
CC 1-1 (Pharmacology)  
AB Rac-Simendan, (.+-.)-(R,S)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-  
pyridazinyl)phenyl]hydrazono]propanedinitrile, and the levorotatory  
enantiomer levosimendan, are drug candidates intended for the treatment of  
congestive heart failure. An enantiospecific high-performance liq.  
chromatog. (HPLC) method suitable for detn. of the ratio of the enantiomer  
concns. in blood plasma samples was developed. Direct resoln. of the  
enantiomers was achieved by using a chiral .beta.-cyclodextrin stationary  
phase in reversed phase mode. With an eluent contg. 24-33% of methanol in  
a 0.5% (vol./vol.) triethylammonium acetate buffer, pH 6.0, and  
a flow rate of 1 mL/min, a resoln. (1.2-1.6) adequate for the detns. was  
achieved. By using UV detection, the relative concn. of the enantiomers  
in plasma was assessed down to 10 ng/mL. For the racemate, the results  
indicated a slightly enantioselective disposition and plasma protein  
binding in rat, dog, and man. The pure enantiomer, levosimendan, was  
found not to isomerize in vivo.

ST simendan enantiomer detn blood HPLC

IT Blood analysis  
HPLC  
(enantiomeric bioanal. of simendan and levosimendan by chiral  
high-performance liq. chromatog.)

IT 131741-08-7, Simendan 141505-33-1, Levosimendan 144238-75-5,  
Dextrosimendan  
RL: ANT (Analyte); ANST (Analytical study)  
(enantiomeric bioanal. of simendan and levosimendan by chiral  
high-performance liq. chromatog.)

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS  
AN 1995:521629 CAPLUS  
DN 122:255986  
TI Troponin C-mediated calcium sensitization induced by levosimendan does not  
impair relaxation  
AU Haikala, Heimo; Nissinen, Erkki; ERTemadzadeh, Ehsan; Levijoki, Jouko;  
Linden, Inge-Britt  
CS Orion-Farmos, Orion Research, Espoo, Finland  
SO Journal of Cardiovascular Pharmacology (1995), 25(5), 794-801  
CODEN: JCPCDT; ISSN: 0160-2446



PB Lippincott-Raven  
DT Journal  
LA English  
CC 1-8 (Pharmacology)  
AB Levosimendan is a novel pos. inotropic drug targeted to increase contraction force of the heart through its calcium-dependent binding to troponin C (cTnC). We investigated the calcium-sensitizing effect of levosimendan on contractile proteins as well as its pos. inotropic and lusitropic effects in paced guinea pig papillary muscle. We also studied the effect on energy consumption of myosin-actin crossbridges in a myosin ATPase assay. The calcium sensitization induced by levosimendan in fibers skinned with saponin was dependent on the perforation velocity of cell membranes. Levosimendan was almost ineffective in slowly perforated fibers, but it was the most potent calcium sensitizer in fibers with rapidly perforated cells. The perforation-dependent calcium sensitization was probably due to changes in phosphorylation state of contractile proteins during the slow dissection of fibers. It is noteworthy that the calcium-sensitizing effect of levosimendan was not affected by acidic pH. Levosimendan at the therapeutically relevant (0.3-10 .mu.M) concns. markedly increased calcium sensitivity both at pH 6.7 and 7.0, being more potent than EMD 53998, pimobendan, and MCI-154. The lack of effect of levosimendan on max. tension supports the hypothesis that levosimendan increases calcium sensitivity through its action on cTnC. Unlike EMD 53998, levosimendan did not increase myosin ATPase activity, indicating that it did not increase the cycling rate of myosin-actin crossbridges. In paced papillary muscles, levosimendan induced pos. inotropic effect without changing relaxation time. Thus, levosimendan was devoid of the main neg. factors described for calcium sensitizers.

ST inotropic levosimendan calcium sensitization heart relaxation; troponin C levosimendan calcium sensitization heart

IT Troponins  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(troponin C-mediated calcium sensitization induced by inotropic drug levosimendan does not impair relaxation of heart muscles)

IT Cardiotonics  
(inotropics, troponin C-mediated calcium sensitization induced by inotropic drug levosimendan does not impair relaxation of heart muscles)

IT 74150-27-9, Pimobendan 98326-33-1, MCI-154 120223-04-3, EMD 53998  
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(calcium sensitization by inotropics and heart muscle relaxation)

IT 141505-33-1, Levosimendan  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(troponin C-mediated calcium sensitization induced by inotropic drug levosimendan does not impair relaxation of heart muscles)

IT 7440-70-2, Calcium, biological studies  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(troponin C-mediated calcium sensitization induced by inotropic drug levosimendan does not impair relaxation of heart muscles)

=> fil uspatful  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
42.38	52.71

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION

CA SUBSCRIBER PRICE

-5.21

-5.21

FILE 'USPATFULL' ENTERED AT 11:37:04 ON 27 MAY 2003

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 May 2003 (20030527/PD)

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HIGHEST GRANTED PATENT NUMBER: US6571393

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CA INDEXING IS CURRENT THROUGH 27 May 2003 (20030527/UPCA)

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>>> USPAT2 is now available. USPATFULL contains full text of the <<<  
>>> original, i.e., the earliest published granted patents or <<<  
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>>> publications, starting in 2001, for the inventions covered in <<<  
>>> USPATFULL. A USPATFULL record contains not only the original <<<  
>>> published document but also a list of any subsequent <<<  
>>> publications. The publication number, patent kind code, and <<<  
>>> publication date for all the US publications for an invention <<<  
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<  
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>>> /PK, etc. <<<

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>>> classifications, or claims, that may potentially change from <<<  
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

=> s l1

L6 10 L1

=> s l6 and pH

339138 PH

L7 8 L6 AND PH

=> d l7 1-8 hit

L7 ANSWER 1 OF 8 USPATFULL

DETD The apparatus comprised a Gilson ASTED (Automated Sequential Trace  
Enrichment System) system (Gilson Medical Electronics, Villiers-le-Bel,  
France). The dialysis cell was fitted with a Cuprophane cellulose  
membrane with a molecular cut-off of 15 kDa and the trace enrichment  
column was a Hypersil ODS (5.8.times.4.6 mm i.d., 10 .mu.m). The  
chromatographic system consisted of an LKB Model 2150 pump (Bromma,  
Sweden) and a Lichrosorb RP-18 (250.times.4 mm i.d., 10 .mu.m) column  
(Merck, Darmstadt, Germany). The detector was a Spectra 100 UV-VIS  
(Spectra-Physics, San Jose, Calif., USA). The wavelength was 380 nm. The  
mobile phase consisted of a 32 mM monosodium dihydrogen phosphate  
buffer, methanol, and tetrahydrofuran (45:65:1, v/v/v, pH  
3.5). The mobile phase flow rate was 1.0 ml/min.

DETD The release of levosimendan from the preparations was studied using the  
paddle method according to USP XXII. The dissolution medium was  
phosphate buffer pH 5.8. The rotation speed of the paddles 50  
rpm.

IT 141505-33-1, Levosimendan

(transmucosal formulations of levosimendan)

L7 ANSWER 2 OF 8 USPATFULL

DETD 100 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone was added to 2997 ml of ethyl acetate, 94.4 ml of water, 77.8 g of D-tartaric acid and 1.0 g of D-tartaric salt of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone under nitrogen. The mixture was stirred in 25.degree. C. for 1.5 h. The mixture was then heated to 65.degree. C. and stirred for 2 h. The precipitate was filtered hot and washed with 561 ml of ethyl acetate. The precipitate was mixed with 400 ml of water and pH of the mixture was adjusted to 9-10 with NH<sub>3</sub>. The mixture was cooled to 0.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 322 ml of cold water and dried in vacuum in 50.degree. C. Yield was 35 g and the ratio of (-/+ ) enantiomers 93/7%. The product (35 g) was further added to 777 ml of acetonitrile and 2.0 g of celite under nitrogen. The precipitate was filtered hot and washed with 33 ml of acetonitrile which was added to the filtrate. 253 ml of acetonitrile was distilled from the filtrate and the remaining mixture was cooled to -5.degree. C. The precipitate was filtered, washed with 76 ml of acetonitrile and dried in vacuum in 50.degree. C. Yield 24.5 g. Ratio of (-/+ ) enantiomers 96/4%.

DETD The enantiomeric purities of the products were determined by the high performance liquid chromatography (HPLC). The enantiomers of compound (II) were separated by using a cellulose-type chiral column (Chiralcel OJ 25.times.0.46 cm). The mobile phase consisted of ethanol. The flow rate was 0.5 ml/min. The enantiomers of compound (I) were separated by using a .beta.-cyclodextrin column (Cyclobond I Beta, 4.6.times.250 mm). The mobile phase consisted of 36% methanol in water buffered to pH 6.0 with 1% triethylammonium acetate. The flow rate was 0.8 ml/min.

IT 141505-33-1P, Levosimendan

(oral compns. contg. cryst. levosimendan for treatment of congestive heart disease)

L7 ANSWER 3 OF 8 USPATFULL

DETD The product of a levosimendan batch is preferably analyzed using High Pressure Liquid Chromatography (HPLC). Suitable apparatus include e.g. C-8 reversed phase HPLC column with UV-detection at 360 nm. The mobile phase is e.g. a mixture of phosphate buffer pH 2.1 and acetonitrile. The levosimendan sample is dissolved in suitable solvent such as a mixture of dimethyl sulfoxide, methanol and water. The reference solutions are prepared by dissolving compound (I) in suitable solvent. The retention times of levosimendan and compound (I) or diastereomers thereof are determined in the chromatographic conditions used. The amount of (I) in the levosimendan sample is determined by comparing the chromatograms obtained for the sample solution and the reference solution. The procedure is described in detail in Example 2.

DETD The HPLC (High Pressure Liquid Chromatography) method for analysis of compound (I) in levosimendan raw material was based on the C-8 reversed phase HPLC column with UV-detection at 360 nm. The mobile phase consisted of acetonitrile and phosphate buffer pH 2.1.

DETD 4. Phosphate buffer pH 2.1:

DETD Dissolve 1.8 g of sodium dihydrogen phosphate (NaH<sub>2</sub>PO<sub>4</sub>) in water and add 2.0 ml of phosphoric acid. Adjust the pH if necessary with 2 M sodium hydroxide or 1 M phosphoric acid. Dilute to 1000.0 ml with water.

DETD

Apparatus Liquid chromatograph

Detector UV-VIS, detection wavelength 360 nm

Column Symmetry C 8, 3.0 .mu.m, 7.5 cm .times. 4.6 mm

Oven temperature ambient

Mobile phase A: phosphate buffer pH 2.1

B: acetonitrile  
 % B 0 min 20%  
     5 min 30%  
    15 min 30%  
    30 min 90%  
 Flow rate 0.8 ml/min  
 Injection volume 100 .mu.l  
 Run time 30 min  
 Post time 10 min  
 Retention times: levosimendan about 13 min  
     Compound (I) minor diastereomer: about 24 min  
     Compound (I) major diastereomer: about 25 min  
 IT 141505-33-1, Levosimendan  
     (ref. compd. for use in anal. of levosimendan batches)

L7 ANSWER 4 OF 8 USPATFULL

SUMM The preparation according to the invention may also include an antimicrobial agent, a preservative, an antioxidant and a pH -controlling agent and other additives known in the art.

DETD Transdermal penetration of levosimendan across human skin in vitro was studied with side-by-side diffusion chambers (DC-100, Crown Glass Co., Somerville, N.J.) at 25.degree. C. The receiver phase (3 ml) consisted of blank sodium phosphate buffer (pH 5.0). Each studied saturated levosimendan solution (3 ml) was added to the donor side. Levosimendan permeation from the gel-formulation was studied with Franz -diffusion chambers (DC-400, Crown Glass Co., Somerville, N.J.) at 25.degree. C. The volume of donor and receiver phases were 1 ml and 5 ml, respectively. Samples were withdrawn up to 72 h at fixed intervals and levosimendan concentration in samples was determined by HPLC (Beckman System Gold, Beckman Instruments Inc., CA). The HPLC column used was LiChrosorb RP-18 (7 .mu.m, 250 mm.times.4 mm), and the mobile phase was 55% of methanol and 45% of sodium phosphate buffer at pH 2.1. Detection wavelength was 360 nm and flow rate was 1.2 ml per min. Trans-dermal flux of levosimendan (.mu.g/h per cm.sup.2) across the skin was calculated using linear regression of the straight-line portion of drug permeation vs. time curve, and dividing by the surface area of the skin (0.64 cm.sup.2).

DETD TABLE 1

Permeation of levosimendan across human skin in vitro. Donor formulations buffered to pH 5 with sodium phosphate buffer. SLS = sodium lauryl sulphate, PG = propylene glycol, OA = oleic acid. % = % m/V.

Donor formulation	Conc. mg/ml	pH	Flux .+- SD	Lag time
			.mu.g/cm.sup.2	h h
water + 90% ethanol	3.66	5.0	7.05 .+- 1.11	15
water + 40% ethanol	1.73	5.0	0.87 .+- 0.21	15
water + 10% ethanol + 0.061 0.01% SLS		5.0	0.43 .+- 0.09	15
water + 10% ethanol + 0.061 0.01% SLS		5.0	0.48 .+- 0.15	15
HPMC-gel (2.5%)				
water + 10% ethanol + 1.19 40% PG + 5% OA		5.0	16.0 .+- 1.62	15
water + 0.1% SLS	0.061	5.0	5.25 .+- 0.96	20
water + 1% SLS	0.49	5.0	25.38 .+- 5.46	20

DETD Electrodes for iontophoresis were prepared from silver wire and silver chloride (Aldrich-Chemie, Steinheim, Germany). Direct current (0.5 mA/cm.sup.2) during iontophoresis was delivered by HP 6181C DC current source (Hewlett-Packard, CA) from the electrodes to the diffusion chambers via salt bridges. Salt bridges were prepared by injecting 1 M NaCl-gel (3% agar) inside plastic tubing (diameter 4 mm, length 15 cm).

Salt bridges prevented direct contact and possible reactions of levosimendan with Ag/AgCl-electrodes. HEPES-buffer at pH 7.4 was used in the receiver phase. Saturated levosimendan solution (3 ml) in HEPES-buffer (pH 7.4) was added to the donor side. AgCl-cathode was connected via the salt bridge to the donor solution. Positive silver anode was connected via the salt bridge to the receiver solution. The chambers were connected in series as constant DC-current was used. The Ag/AgCl-electrodes could be used continuously for 12 h. The results of this experiment are summarized in Table 2.

DETD TABLE 2

Penetration of levosimendan across human skin in vitro by iontophoresis (constant current 0.5 mA/cm.<sup>sup.2</sup>).

Donor solution	Conc. mg/ml	pH	Flux .+- . SD	Lag time h h
HEPES- buffer	0.41	7.4	2.87 .+- . 0.57	2

IT 141505-33-1, Levosimendan

(transdermal compns. contg. levosimendan for treatment of heart failure)

L7 ANSWER 5 OF 8 USPATFULL

DETD The enantiomeric purities of the products were determined by the high performance liquid chromatography (HPLC,). The enantiomers of compound (II) were separated by using a cellulose-type chiral column (Chiralcel OJ 25.times.0.46 cm). The mobile phase consisted of ethanol. The flow rate was 0.5 ml/min. The enantiomers of compound (I) were separated by using a .beta.-cyclodextrin column (Cyclobond I Beta, 4.6.times.250 mm). The mobile phase consisted of 36% methanol in water buffered to pH 6.0 with 1% triethylammonium acetate. The flow rate was 0.8 ml/min.

DETD 100 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone was added to 2997 ml of ethyl acetate, 94,4 ml of water, 77,8 g of D-tartaric acid and 1.0 g of D-tartaric salt of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone under nitrogen. The mixture was stirred in room temperature for 1.5 h. Thereafter the mixture was heated to 65.degree. C. and stirred for 2 h. The precipitate was filtered hot and washed with 561 ml of ethyl acetate. The precipitate was mixed with 400 ml of water and pH of the mixture was adjusted to 9-10 with NH.sub.3. The mixture was cooled to 0.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 322 ml of cold water and dried in vacuum in 50.degree. C. Yield was 35 g and the ratio of (-/+ ) enantiomers 93/7%. The product (35 g) was further added to 777 ml of acetonitrile and 2.0 g of celite under nitrogen. The precipitate was filtered hot and washed with 33 ml of acetonitrile which was added to the filtrate. 253 ml of acetonitrile was distilled from the filtrate and the remaining mixture was cooled to -5.degree. C. The precipitate was filtered, washed with 76 ml of acetonitrile and dried in vacuum in 50.degree. C. Yield 24.5 g. Ratio of (-/+ ) enantiomers 96/4%.

DETD 50 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone was added to 1500 ml of ethyl acetate, 46 ml of water, 37.5 g of D-tartaric acid and 1.0 g of D-tartaric salt of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone. The mixture was stirred in room temperature for 1.5 h. Thereafter the mixture was heated to 65.+- .3.degree. C. and stirred for 3 h. The precipitate was filtered hot and washed with 116 ml of ethyl acetate of room temperature. The precipitate was mixed with 200 ml of water of room temperature and 44 g of potassium bicarbonate in 90 ml of water was slowly added. It was checked that pH was over 9.0. The mixture was cooled to 0.+- .3.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 120 ml of cold water and dried in vacuum in 50.+- .5.degree. C. Yield 17.87 g. Ratio of (-/+ ) enantiomers 90.7/8.6%.

DETD 50 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-

pyridazinone was added to 1500 ml of ethyl acetate, 45 ml of water and 37.3 g of L-tartaric acid. The mixture was heated to 60.degree. C. and stirred for 2 h. The precipitate was filtered and the filtrate was cooled to -10.degree. C. and kept in this temperature for 2 h. The precipitate that crystallized from the filtrate was filtered and dried in vacuum in 50.degree. C. The precipitate was mixed with 200 ml of water in room temperature and 43 g of potassium bicarbonate in 90 ml of water was slowly added. It was checked that pH was over 9.0. The mixture was cooled to 0.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 120 ml of cold water and dried in vacuum in 50.+-.5.degree. C. Yield 20.61 g. Ratio of (-/+ enantiomers 78.7/21.2%.

IT 131741-08-7P 141505-33-1P

(method for obtaining pure enantiomer of a pyridazinone deriv.)

L7 ANSWER 6 OF 8 USPATFULL  
SUMM TABLE 1

The water solubility of (-) enantiomer and racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) in 67 mM phosphate buffer (pH 2).  
Compound Solubility (mg/ml)

(-) enantiomer	0.029
racemic	0.0007

DETD The optical purities of the compounds were determined by the high performance liquid chromatography. The instrument was a Waters 600 E gradient pump with a Waters 991 photodiode array detector and a Waters 700 Satellite Wisp injector (Millipore Co.) controlled by a NEC Powermate SX Plus computer. The enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one were separated by using a cellulose-type chiral column (Chiracel=OJ, 4.6.times.250 mm, Daicel Chemical Industries LTD.). The mobile phase consisted of 97% 2-propanol and 3% hexane. The flow rate was 0.3 ml/min. The enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile were separated by using a .beta.-cyclodextrin column (Cyclobond 1b, 4.6.times.250 mm, Advance Separation Technologies Inc.). The mobile phase consisted of 41% methanol in water buffered to pH 4.0 with 1% triethylammonium acetate. The flow rate was 0.3 ml/min.

IT 141505-33-1P 144238-75-5P

(prepn. of, as cardiovascular agent)

L7 ANSWER 7 OF 8 USPATFULL  
SUMM TABLE 1

The water solubility of (-) enantiomer and racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) in 67 mM phosphate buffer (pH 2).  
Compound Solubility (mg/ml)

(-) enantiomer	0.029
racemic	0.0007

DETD The optical purities of the compounds were determined by the high performance liquid chromatography. The instrument was a Waters 600 E gradient pump with a Waters 991 photodiode array detector and a Waters 700 Satellite Wisp injector (Millipore Co.) controlled by a NEC Powermate SX Plus computer. The enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one were separated by using a cellulose-type chiral

column (Chiracel=OJ, 4.6.times.250 mm, Daicel Chemical Industries LTD.). The mobile phase consisted of 97% 2-propanol and 3% hexane. The flow rate was 0.3 ml/min. The enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile were separated by using a .beta.-cyclodextrin column (Cyclobond lb, 4.6.times.250 mm, Advance Separation Technologies Inc.). The mobile phase consisted of 41% methanol in water buffered to pH 4.0 with 1% triethylammonium acetate. The flow rate was 0.3 ml/min.

IT 141505-33-1P 144238-75-5P  
(prepn. of, as cardiovascular agent)

L7 ANSWER 8 OF 8 USPATFULL  
DETD TABLE 1

The water solubility of (-) enantiomer and racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (1) in 67 mM phosphate buffer (pH 2).  
Compound Solubility (mg/ml)

(-) enantiomer	0.029
racemic	0.0007

DETD The optical purities of the compounds were determined by the high performance liquid chromatography. The instrument was a Waters 600 E gradient pump with a Waters 991 photodiode array detector and a Waters 700 Satellite Wisp injector (Millipore Co.) controlled by a NEC Powermate SX Plus computer. The enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one were separated by using a sellulose-type chiral column (Chiracel-OJ, 4.6.times.250 mm, Daicel Chemical Industries LTD.). The mobile phase consisted of 97% 2-propanol and 3% hexane. The flow rate was 0.3 ml/min. The enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile were separated by using a .beta.-cyclodextrin column (Cyclobond lb, 4.6.times.250 mm, Advance Separation Technologies Inc.). The mobile phase consisted of 41% methanol in water buffered to pH 4.0 with 1% triethylammonium acetate. The flow rate was 0.3 ml/min.

IT 141505-33-1P 144238-75-5P  
(prepn. of, as cardiovascular agent)

=> d 17 1-8

L7 ANSWER 1 OF 8 USPATFULL  
AN 2002:129969 USPATFULL  
TI Transmucosal formulations of levosimendan  
IN Kurkela, Kauko, Espoo, FINLAND  
Marvola, Martti, Helsinki, FINLAND  
Larma, Ilkka, Springfield, NJ, United States  
Virtanen, Raimo, Rusko, FINLAND  
Karlsson, Marianne, Helsinki, FINLAND  
PA Orion Corporation, Espoo, FINLAND (non-U.S. corporation)  
PI US 6399610 B1 20020604  
WO 9932081 19990701  
AI US 2000-581610 20000831 (9)  
WO 1998-FI977 19981211  
20000831 PCT 371 date  
PRAI FI 1997-4578 19971219  
DT Utility  
FS GRANTED  
LN.CNT 281  
INCL INCLM: 514/249.000  
INCLS: 424/434.000; 424/435.000; 424/449.000; 424/451.000; 424/464.000

NCL NCLM: 514/249.000  
NCLS: 424/434.000; 424/435.000; 424/449.000; 424/451.000; 424/464.000  
IC [7]  
ICM: A61K031-50  
ICS: A61K009-14; A61F013-02  
EXF 514/247; 424/449; 424/434; 424/451; 424/464; 424/435  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 2 OF 8 USPATFULL  
AN 2002:50635 USPATFULL  
TI Oral compositions of levosimendan  
IN Backman, Maarit, Helsinki, FINLAND  
Larma, Ilkka, Springfield, NJ, United States  
Antila, Saila, Helsinki, FINLAND  
Lehtonen, Lasse, Espoo, FINLAND  
PA Orion Corporation, Espoo, FINLAND (non-U.S. corporation)  
PI US 6355269 B1 20020312  
WO 9916443 19990408  
AI US 2000-509205 20000608 (9)  
WO 1998-FI753 19980924  
20000608 PCT 371 date  
PRAI FI 1997-3804 19970926  
DT Utility  
FS GRANTED  
LN.CNT 294  
INCL INCLM: 424/464.000  
INCLS: 514/247.000; 544/239.000  
NCL NCLM: 424/464.000  
NCLS: 514/247.000; 544/239.000  
IC [7]  
ICM: A61K009-20  
ICS: A61K031-50; C07D237-02  
EXF 424/464; 514/247; 544/239  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 8 USPATFULL  
AN 2002:14077 USPATFULL  
TI Reference compound for use in the analysis of levosimendan batches  
IN Backstrom, Reijo, Helsinki, FINLAND  
Heinonen, Tuula, Espoo, FINLAND  
Hauta-Aho, Tuula, Vantaa, FINLAND  
PA Orion Corporation, Espoo, FINLAND (non-U.S. corporation)  
PI US 6340764 B1 20020122  
WO 9965888 19991223  
AI US 2001-719806 20010220 (9)  
WO 1999-FI539 19990618  
20010220 PCT 371 date  
PRAI FI 1998-1428 19980618  
DT Utility  
FS GRANTED  
LN.CNT 266  
INCL INCLM: 549/321.000  
INCLS: 514/473.000; 552/001.000; 436/098.000; 436/093.000  
NCL NCLM: 549/321.000  
NCLS: 436/093.000; 436/098.000; 552/001.000  
IC [7]  
ICM: C07D307-32  
ICS: G01N030-04; C07C247-00  
EXF 549/321; 514/473  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 8 USPATFULL  
AN 2001:18019 USPATFULL  
TI Transdermal compositions containing levosimendan



IN Urtti, Arto, Kuopio, Finland  
 Hirvonen, Jouni, Vantaa, Finland  
 Lehtonen, Lasse, Espoo, Finland  
 Antila, Saila, Helsinki, Finland  
 PA Orion Corporation, Espoo, Finland (non-U.S. corporation)  
 PI US 6183771 B1 20010206  
 WO 9801111 19980105  
 AI US 1999-214295 19990323 (9)  
 WO 1997-FI412 19970626  
 19990323 PCT 371 date  
 19990323 PCT 102(e) date  
 PRAI GB 1996-14098 19960705  
 DT Utility  
 FS Granted  
 LN.CNT 251  
 INCL INCLM: 424/449.000  
 INCLS: 424/448.000; 424/484.000; 424/486.000  
 NCL NCLM: 424/449.000  
 NCLS: 424/448.000; 424/484.000; 424/486.000  
 IC [7]  
 ICM: A61F013-02  
 ICS: A61K009-70; A61K009-14  
 EXF 424/402; 424/448; 424/449; 424/484; 424/486; 514/846  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 5 OF 8 USPATFULL  
 AN 2001:14644 USPATFULL  
 TI Method for obtaining pure enantiomers of a pyridazinone derivative  
 IN Timmerbacka, Mika, Veikkola, Finland  
 Lehtonen, Jorma, Kuohu, Finland  
 Tanninen, Veli Pekka, Espoo, Finland  
 Muttonen, Esa, Helsinki, Finland  
 Kaukonen, Jukka, Helsinki, Finland  
 Hyppola, Riikka, Espoo, Finland  
 Backstrom, Reijo, Helsinki, Finland  
 PA Orion Corporation, Espoo, Finland (non-U.S. corporation)  
 PI US 6180789 B1 20010130  
 WO 9735841 19971002  
 AI US 1999-155294 19990204 (9)  
 WO 1997-FI196 19970327  
 19990204 PCT 371 date  
 19990204 PCT 102(e) date  
 PRAI FI 1996-6474 19960327  
 DT Utility  
 FS Granted  
 LN.CNT 498  
 INCL INCLM: 544/239.000  
 INCLS: 514/247.000  
 NCL NCLM: 544/239.000  
 IC [7]  
 ICM: A61K031-50  
 ICS: C07D237-14  
 EXF 514/247; 544/239  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 6 OF 8 USPATFULL  
 AN 96:99209 USPATFULL  
 TI (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-  
 hydrazono]propanedinitrile  
 IN Nore, Pentti, Helsinki, Finland  
 Honkanen, Erkki, Espoo, Finland  
 Backstrom, Reijo, Helsinki, Finland  
 Wikberg, Tom, Espoo, Finland  
 Haikala, Heimo, Espoo, Finland

Haarala, Jorma, Helsinki, Finland  
 PA Orion-yhtymä Oy, Espoo, Finland (non-U.S. corporation)  
 PI US 5569657 19961029  
 AI US 1995-454856 19950531 (8)  
 RLI Division of Ser. No. US 1993-81360, filed on 30 Jun 1993, now patented,  
 Pat. No. US 5424428, issued on 13 Jun 1995  
 PRAI GB 1991-49 19910103  
 GB 1991-189473 19910905  
 DT Utility  
 FS Granted  
 LN.CNT 262  
 INCL INCLM: 514/247.000  
 INCLS: 544/239.000  
 NCL NCLM: 514/247.000  
 NCLS: 544/239.000  
 IC [6]  
 ICM: A61K031-50  
 EXF 544/239; 514/247  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 7 OF 8 USPATFULL  
 AN 96:36567 USPATFULL  
 TI (-) [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydra-  
 zono]propanedinitrile  
 IN Nore, Pentti, Helsinki, Finland  
 Honkanen, Erkki, Espoo, Finland  
 Backstrom, Reijo, Helsinki, Finland  
 Wikberg, Tom, Espoo, Finland  
 Haikala, Heimo, Espoo, Finland  
 Haarala, Jorma, Helsinki, Finland  
 PA Orion-yhtymä Oy, Espoo, Finland (non-U.S. corporation)  
 PI US 5512571 19960430  
 AI US 1995-455035 19950531 (8)  
 RLI Division of Ser. No. US 1993-81360, filed on 30 Jun 1993, now patented,  
 Pat. No. US 5424428, issued on 13 Jun 1995  
 PRAI GB 1991-49 19910103  
 GB 1991-18947 19910905  
 DT Utility  
 FS Granted  
 LN.CNT 253  
 INCL INCLM: 544/239.000  
 NCL NCLM: 544/239.000  
 IC [6]  
 ICM: C07D037-14  
 EXF 544/239  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 8 OF 8 USPATFULL  
 AN 95:52470 USPATFULL  
 TI (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-  
 hydrazono]pr  
 IN Nore, Pentti, Helsinki, Finland  
 Honkanen, Erkki, Espoo, Finland  
 Backstrom, Reijo, Helsinki, Finland  
 Wikberg, Tom, Espoo, Finland  
 Haikala, Heimo, Espoo, Finland  
 Haarala, Jorma, Helsinki, Finland  
 PA Orion-yhtymä Oy, Espoo, Finland (non-U.S. corporation)  
 PI US 5424428 19950613  
 WO 9212135 19920723  
 AI US 1993-81360 19930630 (8)  
 WO 1992-FI3 19920103  
 19930630 PCT 371 date  
 19930630 PCT 102(e) date

PRAI GB 1991-49 19910103  
GB 1991-18947 19910905  
DT Utility  
FS Granted  
LN.CNT 284  
INCL INCLM: 544/239.000  
NCL NCLM: 544/239.000  
IC [6]  
ICM: C07D037-14  
EXF 544/239; 514/247  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L5 8 S L4 AND PH

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L6 10 S L1  
L7 8 S L6 AND PH

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